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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/699,362	10/31/2003	Ivan Svendsen	6600.200-US	3030

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EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 09/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/699,362	SVENDSEN ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-7,11,15,17 and 30-32* is/are pending in the application.

4a) Of the above claim(s) *17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-7, 11, 15, and 30-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and response received June 29, 2006 is acknowledged.
Claims 2, 3, 8-10, 12-14, 16, 18-29, and 33 have been canceled.
Claims 1, 4-7, 11, 15, 17, 30, and 32 have been amended.
Claims 1, 4-7, 11, 15, 17, 30, and 32 are pending.
Claim 17 stands withdrawn from consideration as being drawn to a nonelected invention. See 37 CFR 1.142(b) and MPEP § 821.03, for reasons of record set forth in the Office Action mailed September 20, 2005.

Claims 1, 4-7, 11, 15, and 30-32 are under examination as they read on anti-TF antibodies that bind an epitope comprising Trp45 of human tissue factor and cells that produce said antibodies.

2. The declaration of Soren Berg Padkjaer is acknowledged and will be discussed with the rejections of record.

Specification

3. Applicant's amendments to the specification received June 29, 2006 are acknowledged.

Claim Objections

4. The objection to claims 1 and 4-7 has been withdrawn due to applicant's claim amendments received June 29, 2006 which adequately address formal maters indicated in the prior office action, while the objection to claims 13 and 14 is rendered moot by applicant's cancellation of said claims in the response received June 29, 2006.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. The rejection of claims 12, 13, 16, and 33 under 35 U.S.C. 112, second paragraph, as being indefinite is rendered moot by applicant's cancellation of said claims in the response received June 29, 2006.

7. Claims 1, 4-7, 11, 15, and 30-32 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, independent claims 1 and 30 have been amended to recite that the antibody "immunoreacts with an epitope on human tissue factor that comprises Trp45". As such, the recited antibody must bind an epitope which comprises a tryptophan residue located at position 45 of human tissue factor. The claim does not recite a sequence for human tissue factor, and as such the numbering convention used to identify a particular tryptophan as being located at position 45 is not known. It is noted that applicant has amended the specification to state that the phrase "human tissue factor" refers to a polypeptide sequence identified as SEQ ID NO:14. Such an amendment is not a definition because it is not clear to what else the term "human tissue factor" may refer. Incorporation of SEQ ID NO:14 into the independent claims may provide a basis by which position 45 of human tissue factor can be unambiguously identified.

Further, dependent claim 32 recites the limitation "...wherein the cell is a cell derived from a cell line selected from...". The claim as originally filed recited "...wherein the cell is selected from the group consisting of...". The specification does not appear to define what is meant by a cell that is derived from a cell. Does it comprise additional mutations, the presence of transfected genes, altered protein expression profiles, or something altogether different? As such, a skilled artisan would not be reasonably apprised of the metes and bounds of the claimed subject matter.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. The rejection of claims 1 and 8-10 under 35 U.S.C. 112, first paragraph, for lack of enablement has been withdrawn in view of applicant's amendments to the claims received June 29, 2006 which removed recitations of binding affinity ranges and canceled claims 8-10.

10. Claim 32 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant has amended claim 32 to recite the limitation "...wherein the cell *is a cell derived from a cell line* selected from..." while the claim as originally filed recited "...wherein the cell is selected from the group consisting of...". The specification discusses cells for use in the instant invention between line 33 of page 12 to line 12 of page 13, but these passages do not disclose *cells derived from a cell line* or define what is meant by this terminology. Given that the cells are derived from a starting cell, it appears that the claimed cell is now broader in scope than that which is disclosed in the specification and claims as originally filed. Such broadening has introduced new matter into the claims.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent

granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. The rejection of claims 1-4, 6-9, 11, 12, 15, 16, and 30-33 under 35 U.S.C. 102(b) as being anticipated by Wong et al. (US Patent No. 5,986,065, see entire document) has been withdrawn in view of applicant's claim amendments received June 29, 2006.

Specifically, the independent claims have been amended to recite that the epitope bound by the anti-TF antibody comprises residue Trp45 of human tissue factor, and the antibodies disclosed by Wong et al. are not disclosed as binding epitopes that comprise the recited amino acid residue.

13. The rejection of Claims 1-4, 6-9, 11-16, and 30-33 under 35 U.S.C. 102(b) as being anticipated by Kirchhofer et al. (US Patent No. 6,703,494, see entire document) has been withdrawn in view of applicant's claim amendments and the declaration of Soren Berg Padkjaer received June 29, 2006.

Specifically, the independent claims have been amended to recite that the epitope bound by the claimed anti-TF antibody comprises residue Trp45 of human TF. Kirchhofer et al. do not disclose that their antibodies bind epitopes comprising this region. The declaration of Soren Berg Padkjaer states that based upon standard molecular modeling techniques, Trp45 is spatially separated from the epitope recognized by antibodies 6B4, HTF1, and 7G11 of Kirchhofer et al.

This declaration is not fully convincing because the modeled structures may be inaccurate and crystallographic data concerning complexes of TF bound to the antibodies 6B4, HTF1, and 7G11 have not been reported.

However, the disclosure by Kirchhofer et al. in Figures 5A-5C that binding of their antibodies to TF is not disrupted by mutagenesis at position 45 is convincing evidence that these antibodies do not bind an epitope of human TF which comprises Trp45. Especially noteworthy is the disclosure that binding of antibody 7G11 to TF is

not altered by mutation at position 45 of human TF even though mutations at positions 46-51 of human TF strongly disrupt antibody binding. As such it appears that the antibodies of Kirchhofer et al. do not bind to epitopes comprising Trp45 of human TF.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. The rejection of claims 1 and 5 under 35 U.S.C. 103(a) as being unpatentable over Wong et al. (US Patent No. 5,986,065, see entire document) in view of Carney (US Patent 5,081,230, see entire document) has been withdrawn in view of applicant's claim amendments received June 29, 2006.

As discussed above, the antibodies disclosed by Wong et al. do not bind the recited amino acid residue, and as such the rejection does not address all the recited claim limitations.

16. The rejection of claims 1 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirchhofer et al. (US Patent No. 6,703,494, see entire document) in view of Carney (US Patent 5,081,230, see entire document) has been withdrawn in view of applicant's claim amendments received June 29, 2006.

As discussed above, the antibodies disclosed by Kirchhofer et al. do not bind the recited amino acid residue, and as such the rejection does not address all the recited claim limitations.

17. Claims 1, 4, 6, 7, 11, 15, and 30-32 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Edgington et al. (US Patent No. 5,223,427, of record on the IDS received January 29, 2004, see entire document) in view of Queen et al. (US Patent 5,693,762, see entire document).

The office action mailed December 29, 2005 states that:

> Edgington et al. teach mouse monoclonal antibodies that specifically bind to human TF and inhibit the binding FVIIa (see entire document, particularly the abstract, Figure 17, Table 8, and lines 3-7 of column 53). Edgington et al. also teach how to make antibody fragments such as F(ab), $F(ab')_2$, and single chain Fv molecules, and the use of antibodies and fragments of antibodies in pharmaceutical preparations (see particularly from line 30 of column 20 to line 65 of column 21). The monoclonal antibodies were produced by the hybridoma method using cell line P3X63Ag8.653 (see particularly lines 55-66 of column 32). A specific disclosed use for the antibodies of Edgington et al. is to modulate the binding of FVIIa to TF *in vivo* (see particularly from line 35 of column 22 to line 17 of column 24). Epitope mapping studies were conducted, and many antibodies bound non-identical epitopes comprising residues Trp45, Lys46, and Try94 of human TF (see particularly Table 5). These teachings differ from the claimed invention in that Edgington et al. do not teach how to make humanized antibodies and they did not measure the binding affinities of their antibodies.
>
> Queen et al. teaches methods of humanizing mouse monoclonal antibodies (see entire document, particularly the abstract). Administration of nonhuman antibodies to human patients is known to generate unwanted immune responses (such as the HAMA response) due to the immunogenicity of the administered antibody, and humanization offers the advantage of reducing the immunogenicity, increasing the effector function, and increasing the half-life of the administered antibody (see particularly lines 6-27 of column 16). Queen et al. also teach that the affinities of humanized antibodies are at least about $1x10^{-8}$ M and are preferably at lest about $1x10^{-10}$ M (see particularly lines 57-61 of column 10). Methods for making humanized antibody fragments including F(ab), $F(ab')_2$ and single chain Fv molecules are also disclosed (see particularly lines 17-34 of column 11).
>
> Therefore it would have been obvious to a person of ordinary skill in the art to make a humanized antibody from the antibodies taught by Edgington et al. Motivation to do so comes from the teachings of Edgington et al. that their antibodies are to be used for *in vivo* methods of treatment, and the teachings of Queen et al. that humanized antibodies offer the advantages of reduced immunogenicity, increased effector function and increased half-life when administered to patients.
>
> In claim 11 and its dependent claims, it appears that the recitation that the frameworks of the humanized antibody be derived from a human antibody that also binds TF is an attempt to introduce a product by process limitation into the claims. Applicant is reminded that "even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). In the instant case it does not appear that humanized antibody made using the process introduced in claim 11 would generate a product different from a humanized antibody generated using the methods of Queen et al. using the antibodies of Edgington et al. as the starting material, since in both instances the product will be an antibody comprising human Fc domains and non-human CDR sequences in human framework regions.

Applicant's arguments filed June 29, 2006 have been fully considered but they are not persuasive. Applicant argues that the antibodies disclosed by Edgington et al. do not bind an epitope of human TF that comprises Trp45, and that Edgington et al. teach away from the importance of TF epitopes comprising Trp45.

This argument is not convincing because Edgington et al. disclose evidence that 7 of their antibodies bind a peptide consisting of residues 41-49 of human tissue factor (see particularly Table 5). These antibodies are TF9-2C4, TF9-5C7, TF9-9C3, TF9-1B8, TF9-4D11, TF9-5G4, and TF9-9E1, and note that peptide p41-49 comprises Trp45. All of these antibodies inhibit the binding of FVIIa to TF and inhibit coagulation (see particularly lines 3-7 of column 53 and Table 8).

The rejection of record is maintained.

18. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Edgington et al. (US Patent No. 5,223,427, of record) in view of Queen et al. (US Patent 5,693,762, of record) as applied to claims 1, 4, 6, 7, 11, 15, 30, and 31 above, and further in view of Carney (US Patent 5,081,230, of record, see entire document).

The teachings of Edgington et al. in view of Queen et al. have been discussed above. These teachings differ from the claimed invention in that $F(ab)_2$ fragments are not disclosed.

Carney teaches methods of making antibody fragments such as $F(ab)_2$, and teaches that and advantage enjoyed by $F(ab)_2$ fragments as compared to whole antibodies is that they have less nonspecific background activity and are less immunogenic *in vivo* (see entire document, particularly lines 1-20 of column 9).

Therefore, a person of ordinary skill in the art at the time the invention was made would have been motivated to make $F(ab)_2$ fragments from the antibodies taught by Edgington et al. that have been humanized by the methods of Queen et al. in order to gain the advantages of reduces nonspecific activity and reduced immunogenicity when administered *in vivo* as taught by Carney.

19. No claims are allowable.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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9/1/06
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